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Themed Issue: Population Pharmacokinetics - A Memorial Tribute To Lewis Sheiner, M.D.
Guest Editors - Peter Bonate and Diane Mould

On Some "Disadvantages" of the Population Approach

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ABSTRACT

In a seminal article on population pharmacokinetic modeling, researchers demonstrated how means and variances of pharmacokinetic parameters for a patient population could be inferred from sparse data collected under conditions of routine patient care. But they also identified 4 potential concerns about their methodology: unobserved confounding variables may bias the inferences; conditions under which data are collected may lead to inaccuracies of reporting or recording; correlations among important predictor variables may reduce statistical efficiency; and costs cannot be controlled by principles of study design. Experiences are reviewed that relate to these potential disadvantages. A method is presented for diagnosing the possible presence of confounding. A model is constructed and applied that captures the influences of data inaccuracies. An example of selecting from among correlated covariates is summarized. Finally, a methodology for optimal study design is reviewed and applied to an example.

KEYWORDS: optimal design, variable selection, noncompliance, errors in variables, confounding

INTRODUCTION

In the 1970s, Sheiner et al[1,2] laid the foundations of population pharmacokinetic (PK) modeling. They showed how, with data collected as part of routine patient care, such modeling can estimate the average values of PK parameters and the interindividual variances of those parameters in a patient population. With such sparsely sampled data from patients on digoxin, their methodology produced estimates that were similar to published values derived with traditional methods.

About their new methodology, Sheiner et al[1] wrote: "Its greatest asset is the ability to exploit possibly fragmentary and unstructured data from each individual. . . . Routine patient data can be analyzed . . . Thus values of pharmacokinetic parameters can be assessed in the population in which drugs are to be used."

But they also recognized potential limitations of their new approach, writing that[1]

> . . . the disadvantages of the use of routine data are not insignificant. They are, first, the possibility of bias due to the effects of unknown concomitant variables that are correlated with included variables; second the problem of reliability of the data; third, the problem of statistical inefficiency, due to correlation of the variables; and, fourth, a methodological problem in that the data cannot be deliberately constructed so as to minimize the costs of the analysis.

The objective here is to consider selected aspects of the above 4 "disadvantages." This is not a comprehensive review, but rather a sampling of some recent research and some examples. The 4 concerns will be taken in reverse order.

Deliberately Constructing the Data

The population PK methodology of Sheiner et al[1,2] has found perhaps its most popular application in clinical trials that are part of drug development. Although in routine patient care the data might be constrained to the configuration in which it is found, clinical trials at least sometimes offer the possibility of prespecifying that configuration. Rather than focusing on the minimization of costs through such prespecification, as Sheiner et al[1] couched their concern, consider the inverse problem of maximizing precision at a given cost, that is, for a given number of patients and samples.[3]

Figure 1 displays some real but disguised data collected from a clinical trial where the treatment phase lasted several months, and a single blood sample was collected from each patient at each of up to 3 clinic visits. For 148 patients, there were 373 observations, an average of 2.5 samples per patient. In the figure, lines connect data from the same individual.

Doses were administered orally twice a day at approximate 12-hour intervals. Already by the time of the first sample for each patient, a sufficient number of doses had been administered that PK steady state should have been reached. A 1-compartment model with first-order absorption and elimination described the data adequately. Figure 2 shows

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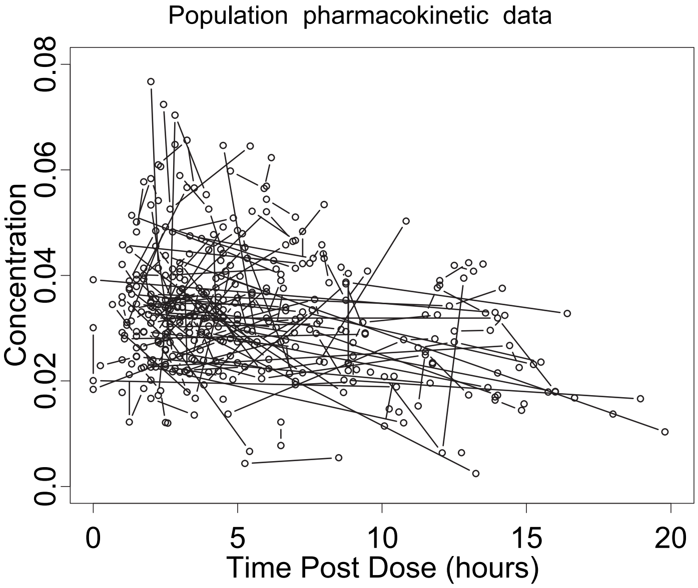

Figure 1. Population pharmacokinetic data.

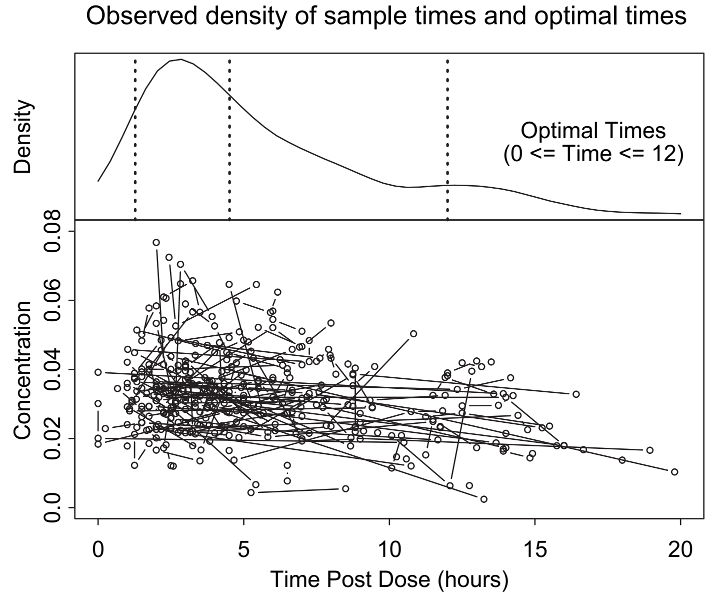

Figure 3. Observed density of sample times and optimal times.

the rise to steady state for such a model dosed regularly at 12-hour intervals.

The steady-state form of the model, available in NONMEM,[4] was fitted to the data in Figure 1. The model was parameterized in terms of the absorption rate constant, k_a, the apparent clearance, Cl, and the apparent volume, V. The resulting parameter estimates (and estimated SEs), as obtained from NONMEM, were 0.74 (0.26), 2.85 (0.09), and 87.6 (20.4), for k_a, Cl, and V, respectively.

The data represented in Figure 1 was collected without controlling the times at which the samples were taken. Patients took their morning doses then visited the clinic at their convenience, at which time blood samples were taken. This lack of control translated into large imprecision

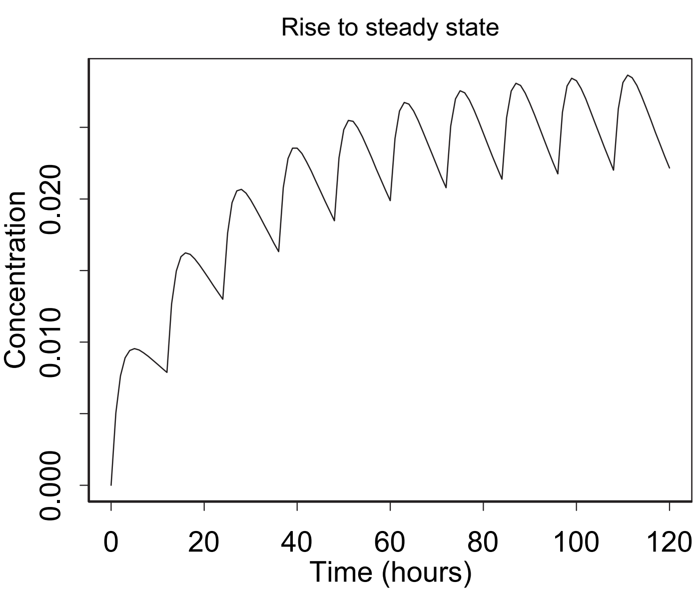

Figure 2. Rise to steady state.

in the estimates of k_a and V, at least relative to the precision of the estimate of Cl.

If it were possible to specify the time postdose for each sample by directing when the patient should visit the clinic, the estimates of k_a and V could have been improved. A methodology for choosing the sampling times has recently been made generally available.[5-8] The methodology is based on approximating and maximizing the determinant of the Fisher Information Matrix.[3] The user must supply a model and provisional estimates for the unknown parameters.

Figure 3 shows the density of observed sampling times and, superimposed on it, the optimal sample times as determined by the methodology. The 1-compartment model and parameter estimates from the fit to the data of Figure 1 were supplied as inputs. The optimal times were determined subject to the constraints that there be 3 samples per subject and that they be $\leq$12 hours postdose.

The methodology also provides the expected SEs of the parameter estimates that would be obtained using the optimized sampling times. Table 1 reports those values. Because the optimization uses an approximation to the Fisher Information Matrix, and NONMEM itself uses an approximation to the log-likelihood, a simulation experiment was run to validate those values. SEs were estimated as SDs of parameter estimates obtained from a sample of 100 simulated data sets. Each data set had the same number of patients and observations as the original, but the sample times were the optimal times identified by the methodology.

Also reported in Table 1 are bootstrap estimates of SEs for the parameter estimates based on the original data. The

Table 1. SEs

Variable	Estimated Via Fit to Original Data	Estimated From 83 Bootstrap Samples of Original Data*	Theoretical Optimum From PFIM_OPT	Estimated From 100 Simulations Using Optimal Times
σ_{k_a}	0.26	0.58	0.10	0.13
σ_{Cl}	0.09	0.10	0.08	0.10
σ_V	20.4	27.3	8.80	10.5

*100 bootstrap samples were generated. SDs are reported based on the 83 samples where NONMEM reported "MINIMIZATION SUCCESSFUL."

results of the bootstrap experiment suggest that the estimate by NONMEM of the SE for k_a was low, but the bootstrap and NONMEM estimates of SEs for Cl and V were similar. The SDs from the simulation experiment were quite close to the predicted SEs from the methodology. For k_a and V, the SEs were reduced substantially with the optimal times relative to the original data.

These results suggest that for a given cost, that is, a given number of patients and observations, precision can be increased by judiciously selecting and prespecifying the times at which samples are collected. However, this conclusion needs some qualification. Open questions remain about robustness of the optimality to inaccuracies in the model and provisional parameter estimates that comprise inputs to the algorithm. Also, in a real clinical trial, sampling times may not readily be controlled precisely to those prespecified. To allow more flexibility, Green and Duffull[9] constructed a design that specified, instead of sampling time points, time windows of which the widths were chosen to allow a loss of statistical efficiency of only 10%. They applied this optimal design in a real clinical trial in parallel with an "empirical," more uniform, distribution of sampling times. Adherence to the prespecified sampling time windows was less than perfect. The optimal-design arm did not outperform the empirical arm on several assessment measures, but it did support identification of a more complex structural model that fit the data better in terms of reduced residual variance.

Correlation of Variables

Correlation of predictor variables, a condition called collinearity in the multiple-regression context, causes imprecise estimation of parameters associated with the predictors.[10] SEs of the parameter estimates are correspondingly large. Such statistical inefficiency of estimation seems to have been the third of the 4 concerns raised by Sheiner et al,[1] as quoted above. But here, the related issue of choosing among correlated predictor variables will be considered. When prior knowledge does not specify what predictor variables belong in a model, and variable-selection methods are used to identify important predictors, collinearity affects the probability of including authentic predictors.[10]

In the population-model context, covariates are the predictor variables of which the correlation causes concern. Identification of covariates that are associated with structural parameters, such as clearance, has been a primary objective of many applications of population modeling. Procedures for selecting covariates have been the subject of much research in recent years.[11-13] They have also generated lively discussions among participants in email discussion lists.[14,15] A recurring theme is that scientific insight should be favored over automatic statistical search procedures but that the latter are, nonetheless, useful tools for exploratory analyses.

For the data discussed in the previous section, the following assessment of covariates was stipulated in the protocol. First, weight was examined as a covariate for clearance, because previous studies of the drug in a different indication had suggested such a relationship. Because it was prespecified, the hypothesis of a relationship between clearance and weight was tested at $\alpha = 0.05$. Next, other covariates, including age, sex, race, creatinine clearance, and several indication-specific covariates, were explored graphically for relationships with patient-specific estimates of clearance and volume derived from an initial model without covariates. Those covariates where some relationship was judged visually evident were then used as candidates in a forward selection procedure with $\alpha = 0.01$ as the criterion to enter the model.

Weight was not significantly related to clearance. Age, sex, and creatinine clearance showed visual evidence of a relationship with clearance. No covariates appeared related to volume. Each of age, sex, and creatinine clearance was significant at $\alpha = 0.01$ when tested individually as a covariate of clearance. First age and then sex was selected for entry into the model based on values of the maximized likelihoods. When age and sex were in the model, creatinine clearance was no longer significant at $\alpha = 0.01$.

Nonetheless, it was ultimately argued that the final model should be one with creatinine clearance as the single covariate influencing drug clearance. The reason was that the drug was known to be cleared via renal and hepatic pathways. Creatinine clearance is highly correlated with age and sex, algebraically so in this case, because the

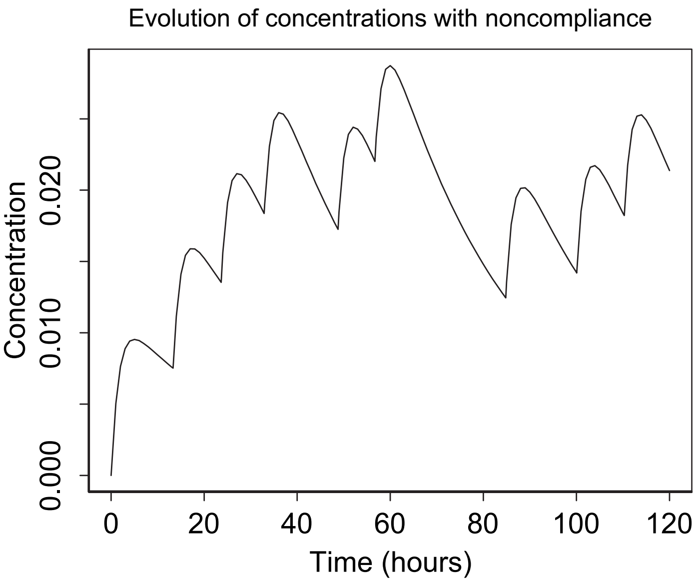

Figure 4. Evolution of concentrations with noncompliance.

Cockroft-Gault estimate of creatinine clearance was used, which is a formula with components including age and sex.[16] The hepatic pathway was not believed to vary markedly with age and sex.

Model building serves multiple objectives: to predict, to explain, to explore, and to test. To satisfy the confluence of objectives, methods have been adopted, such as stepwise variable selection, that confuse the exploratory and confirmatory aspects of data analysis. These methods are attractive, because they offer objectivity, automation, and openness to the unexpected. But they can mislead, especially when the covariates are correlated with one another, so it is important to understand their properties and to seek alternative data analytic paradigms.[11] Because models are always tentative and in need of challenge, mixing prior knowledge and assumptions into the model-building process is both acceptable and necessary.

Reliability of the Data

The depiction in Figure 2 of how concentrations evolve over time is an ideal that is rarely if ever met. It assumes that the patient took a constant dose regularly at exact 12-hour intervals. In the real world, when patients self-administer a drug, they skip doses sometimes, or they may take doses at times that differ from the prescribed regimen. Such deviations are components of noncompliance. Figure 4 depicts what might be a more realistic picture. Moreover, in a clinical trial, the times at which doses are taken may be reported inaccurately.

When a modeler ignores these aspects of noncompliance and faulty reporting, serious biases in the parameter estimates can result.[17-19] Remedies have been proposed, including the use of electronic monitoring systems that record when a patient's medication package has been opened[17] and Bayesian methods of inference that take advantage of some prior knowledge or a subset of fully compliant data.[20,21]

Electronic monitoring systems are still not widely used, and relevant information for a Bayesian approach might not be available. Here, for the data depicted in Figure 1, we will consider directly modeling the various sources of unreliability. We will use the methodology pioneered by Sheiner et al,[1,2] in the current implementation of that methodology as NONMEM.[4]

First, consider a relabeling of the time axis so that the dose before the sample dose is assumed to be at time 0, and assume that this dose is sufficiently long after the start of dosing that the patient PKs should be at steady state (see Figure 5).

Let $C_{ss}(t)$ denote the predicted response of the 1-compartment model t hours after a dose at steady state, assuming regular 12-hour dosing. At the newly translated time 0, a perfectly compliant patient would have expected concentration $C_{ss}(0)$, but a real patient will be modeled as having expected concentration $C_{ss}(0)e^{\eta_{ss}}$, where the exponentiated random effect captures that patient pattern of noncompliance. Letting $\eta_{ss} = \eta_{ss,IIV} + \eta_{ss,IOV}$, both interindividual and interoccasion[22] variation are modeled. Such a generalized notion of steady state has been described by Wang et al.[23] On the new time axis, let the time of the sample be t_{sample}. Then the expected contribution from the dose at time 0 is $C_{ss}(t_{sample})e^{\eta_{ss}}$.

To account for errors in the time variable, consider a "structural relationship model,"[24] where reported dosing time is taken as a second response variable together with

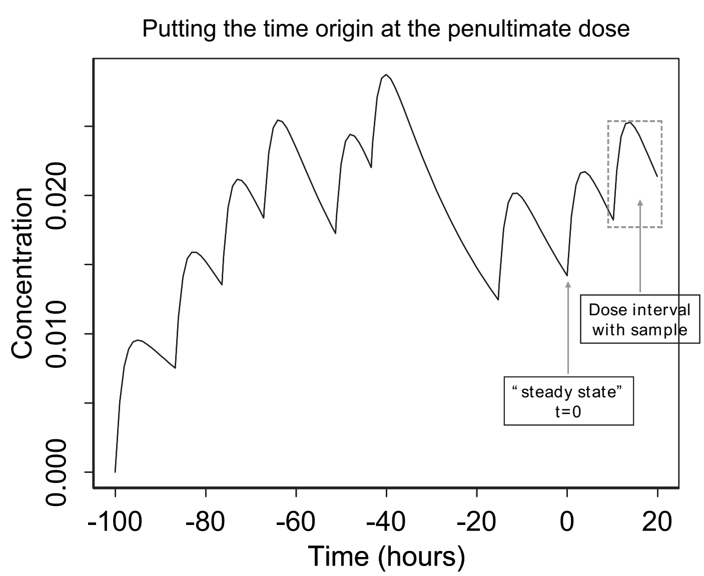

Figure 5. Putting the time origin at the penultimate dose.

the observed concentration. Let μ denote the expected interval between the penultimate and ultimate doses, and let $\eta_D = \eta_{D,IIV} + \eta_{D,IOV}$ represent the deviation from this interval for a patient at an occasion. On the new time axis, the time of the ultimate dose for a patient is $t_{dose}^{true} = \mu + \eta_D$, and the time between that dose and the sample is $t_{postdose} = t_{sample} - t_{dose}^{true}$. The reported time is modeled as a response variable with $t_{dose}^{reported} = t_{dose}^{true} + \varepsilon_D$.

Let $C_1(t_{postdose})$ denote the predicted contribution of the 1-compartment model from a dose taken at t_{dose}^{true}. But such a dose may not have been taken. Let X be an indicator for whether the dose was taken. Model X as

$$X = \frac{\exp(\theta + \eta_X)}{1 + \exp(\theta + \eta_X)}$$

η_X is modeled as an interoccasion random effect. If η_X is large negative, then $X = 0$; if large positive, then $X = 1$. Intermediate values may be interpreted as irresolvable uncertainty about whether the dose was taken. The actual expected contribution from the dose that should have been taken at t_{dose}^{true} is, thus, $XC_1(t_{postdose})$.

Finally, the observed concentration is modeled as $C^{observed} = C_{ss}(t_{sample})e^{\eta_{ss}} + XC_1(t_{postdose}) + \varepsilon_C$. This, together with the usual terms for intersubject variability of k_a, Cl, and V, completes the specification of a model that can be programmed in NONMEM. An example control file is provided in the Appendix.

The model was fitted to the data in Figure 1. The SD of the reporting error for the time response ε_D was fixed, as is common in structural relationship models, to ensure identifiability; different values were tried, eventually settling at 0.95 hours. The expected dosing interval μ was estimated as 11.6 hours. The interpatient component of η_D was judged significant, but not interoccasion variation; the former was estimated to have a SD of 0.83 hours. Thus, according to the model, the average dosing interval was around 12 hours (11.6 hours); each patient had his or her own regular deviation from this average, which was typically around 1 hour (0.83 hours), and the typical deviation of the reported dosing time from the actual was also around 1 hour (0.95 hours).

The interoccasion component of η_{SS} was significant but not the interpatient component. The implied coefficient of variation of predicted steady-state concentrations was 18%.

The inferred distribution of occasion-specific estimates of X was bimodal, with modes at 0 and 1. Figure 6 plots the data with differentiation of points where X was estimated as 0, indicating a missed dose, from 1, indicating a taken dose. Such a diagnostic may lead to additional investigation (eg, checking case record forms for comments or querying study sites) or alternative handling of data points suspected of association with missed doses (eg, refitting the model with those points excluded as a sensitivity check).

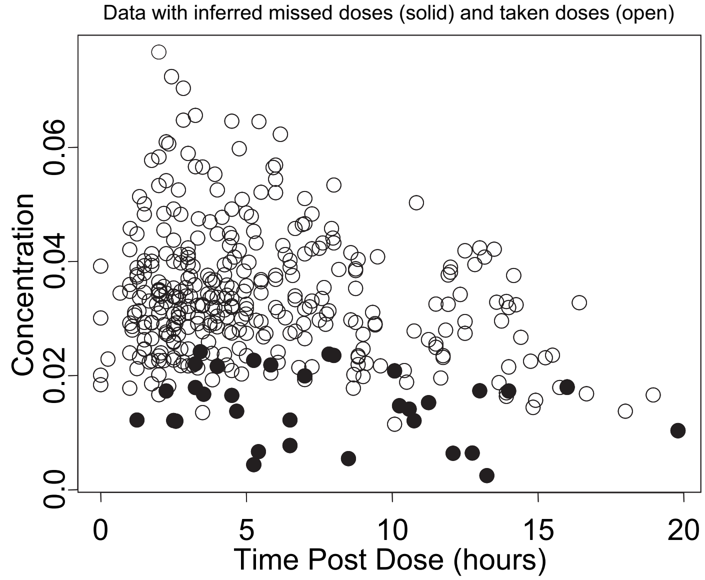

Figure 6. Data with inferred missed doses (solid) and taken doses (open).

The estimated clearance was similar to that found earlier (2.72 vs 2.85 L/h). But the estimated k_a was smaller (0.30 vs 0.74 h^{-1}), as was the estimated volume (60.3 vs 87.6 L).

The model was sensitive to initial guesses for the parameters, and convergence was not always achieved, according to the NONMEM judgment. It would be difficult to examine the properties of such a finicky model by a simulation study. Thus, in retrospect, this example is offered not as a recommended, general approach but rather as a didactic experiment to illustrate some sources of data errors and some modeling components that demonstrate the versatility of NONMEM and that might be found useful in some situations. For example, a similar approach for a design where a single dose is followed by several plasma samples has been explored more systematically by Soy et al.[25] In general, electronic monitoring systems to improve data reliability should be used whenever possible, or other sources of information to allow more refined statistical methodologies, such as the previously cited Bayesian approaches, should be sought.

Unknown Concomitant Variables

We consider an example that concerns the relationship between PKs and clinical outcome, that is, PK/efficacy. The drug treats a chronic condition. The treatment phase of

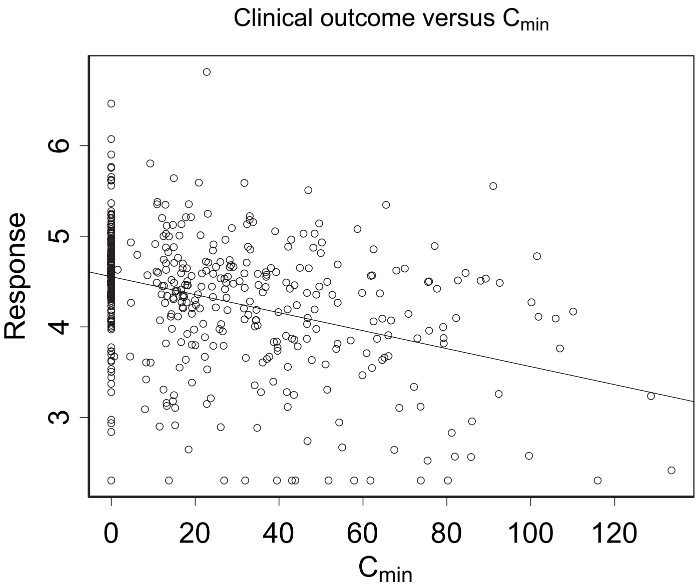

Figure 7. Clinical outcome versus C_{min}.

a clinical trial, where patients were randomized to 1 of 3 drug doses or placebo, spanned several months, during which several steady-state trough concentrations were observed. The average of a patient's trough samples, a variable called C_{min}, was the measure of drug exposure used to predict a single, univariate summary of clinical outcome. Thus, the longitudinal nature of the data was ignored, and the PK/efficacy model was not essentially a population model. But population-model thinking will be seen as helpful to explore the ramifications and possible diagnosis of unknown concomitant variables. Figure 7 displays the data, suggesting that a linear PK/efficacy relationship is reasonable.

The potential problem here is that because patients were randomized to a dose and not prespecified concentrations, C_{min} is an outcome variable, as is the clinical response. Suppose that large values of some unobserved concomitant variable are associated with lower clearance and with a worse clinical outcome. Then patients who have higher concentrations in the dose-controlled trial (because of lower clearance) will tend to have higher values of this variable and, hence, less favorable clinical responses. Had patients been randomized to concentration in a concentration-controlled trial,[26] then at the higher concentrations there would be patients with more diverse values of the unobserved concomitant variable, so there would be more patients at those higher concentrations who have better clinical outcomes. The PK/efficacy relationship inferred from the dose-controlled trial would be biased toward zero relative to that of the concentration-controlled trial. The unobserved concomitant variable in the above scenario is called a confounder, and the biased PK/efficacy inference is called confounded.

Modeling the situation suggests some diagnostics to help assess the possibility of confounding. Let D_i, c_i, and y_i be the randomized dose, observed C_{min}, and observed clinical response for the i'th patient, respectively. Suppose a confounder exists. Denote its value for the i'th patient by η_i, and treat it as a random variable with mean zero. Assume that C_{min} is proportional to dose, and that the PK/efficacy relationship is linear, as suggested by Figure 7. Furthermore, assume that the effect of the confounder is as represented in Equations 1 and 2:

$$\log(c_i) = \alpha_0 + \log(D_i) + \alpha_2\eta_i + \varepsilon_{ci} \tag{1}$$

$$y_i = \beta_0 + \beta_1 c_i + \beta_2\eta_i + \varepsilon_{yi} \tag{2}$$

Thus, η_i affects the slope of the dose/concentration relationship, and it affects the level of the PK/efficacy relationship. Because η_i is unobserved, Equations 1 and 2 are overdetermined and can be reduced to:

$$\log(c_i) = \alpha_0 + \log(D_i) + \zeta_{ci} \tag{3}$$

$$y_i = \beta_0 + \beta_1 c_i + \zeta_{yi} \tag{4}$$

where:

$$\zeta_{ci} = \alpha_2\eta_i + \varepsilon_{ci} \tag{5}$$

$$\zeta_{yi} = \beta_2\eta_i + \varepsilon_{yi} \tag{6}$$

If $\alpha_2 \neq 0$, $\beta_2 \neq 0$, and $\text{var}(\eta_i) \neq 0$, then η_i would contribute to both models, and, hence, in Equation 4, c_i would be correlated with ζ_{yi}. That is, although Equation 4 appears to be a standard, linear-regression model often used for empirical models of PK/pharmacodynamic (PD) relationships, it would really not be such a standard model, because one of the usual assumptions of linear regression, namely, independence of the regressors and the error, would be violated. Because of the correlation between c_i and ζ_{yi}, the

Table 2. PK/Efficacy via Ordinary and Two-Stage Regression

Estimation Method	$\hat{\beta}_0$	$\hat{\beta}_1$	Hausman *P* Value
Ordinary least squares	4.56 ± 0.04	−0.010 ± 0.001	
Two-stage regression	4.58 ± 0.04	−0.011 ± 0.001	0.47

least-squares estimates of β_0 and β_1 would be biased.[27] This bias would be the manifestation of confounding because of the unobserved covariate η_i.

Because patients were randomized to dose, in Equations 3 and 4, D_i is independent of ζ_{yi}. Also, y_i depends on D_i only through c_i. These conditions imply that D_i is an instrumental variable[28] for Equation 4. Instrumental variables can be used to derive estimates of β_0 and β_1 that are consistent, that is, that can be made arbitrarily close to β_0 and β_1 with probability that approaches 1 as the sample size increases.[28] In a procedure called 2-stage regression,[29] one first regresses c_i on D_i and then regresses y_i on the predicted value of c_i. SAS PROC MODEL[30] implements the procedure. It also provides a test, called Hausman's test,[27] for the presence of bias, based on the quantitative differences between the estimates from ordinary regression and 2-stage regression. Table 2 shows the results of applying and comparing the 2 regression approaches. These results suggest that the original PK/efficacy inference is unconfounded, because the 2 sets of estimates are similar, and Hausman's test is not significant.

In PK/PD analysis, the relationship between concentration and response is often assumed to be causal. The meaning of causality is not so easy to pin down,[31] and the estimation of causal relationships with observational data requires care.[32,33] Instrumental variables have been proposed as one tool for causal inference in the presence of confounding.[28] SAS PROC MODEL[30] implements instrumental-variable methods for nonlinear models, also, so that more general PK/PD models might be considered. But researchers still debate the proper approach to instrumental-variable analysis.[34] More consideration of these issues among population modelers is needed.

CONCLUSION

The passage about the 4 "disadvantages" quoted in the Introduction did not end with the simple enumeration of concerns. The authors[1] concluded the paragraph on a positive note:

"The analysis of routine clinical data unquestionably requires greater sophistication in statistics than the analysis of experimental data. We contend, however, that a reasonable effort to develop sophisticated data analysis methods is amply repaid: the problems of data reliability, statistical inefficiency, and methodology can be managed."

Notice, however, that the affirmation does not cover the concern about confounding. The next paragraph continued:[1] "What remains is the ever-present danger of bias due to incompletely controlled concomitants." How to deal with confounding in observational data remained one of Lewis Sheiner's interests. Indeed, he was a consultant for Novartis on the project discussed in the previous section and his insights inspired those results. It is a privilege to dedicate this article to his memory.

ACKNOWLEDGMENTS

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APPENDIX: NONMEM CODE

```
$PROB DATA BRELIABILITY MODEL
$INPUT DV ID TDOS DOSE OCC TSAM CMT
$DATA DATA.CSV IGNORE = #
$PRED
TAU = 12.
TVKA = THETA(1)
KA = TVKA
TVCL = THETA(2)
CL = TVCL*EXP(ETA(1))
TVV = THETA(3)
V = TVV*EXP(ETA(2))
KE = CL/V
;DEFINE INDICATORS FOR OCCASION
X1 = 0
X2 = 0
X3 = 0
IF (OCC.EQ.1) THEN
X1 = 1
ENDIF
IF (OCC.EQ.2) THEN
X2 = 1
ENDIF
IF (OCC.EQ.3) THEN
X3 = 1
ENDIF
;TRUE TIME OF DOSING AND TIME POST DOSE.
;SUBJECT EFFECT PLUS OCCASION EFFECTS.
TDTR = THETA(4) + ETA(3) + X1*ETA(4) +
  X2*ETA(5) + X3*ETA(6)
```

```
TPD = TSAM - TDTR
IF (TPD.LT.0) THEN
TPD = 0.
ENDIF
;CONTRIBUTION FROM HISTORY TO
   STEADY-STATE DOSE.
;SUBJECT EFFECT PLUS OCCASION EFFECTS.
SSKA = EXP(-KA*TSAM)
SSKE = EXP(-KE*TSAM)
DENA = 1. - EXP(-KA*TAU)
DENE = 1. - EXP(-KE*TAU)
DUM = DOSE*KA/V/(KA-KE)*(SSKE/DENE -
   SSKA/DENA)
SSETA = ETA(7) + X1*ETA(8) + X2*ETA(9) +
   X3*ETA(10)
SSCNT = DUM*EXP(SSETA)
;CONTRIBUTION FROM RECORDED DOSE
OBSKA = EXP(-KA*TPD)
OBSKE = EXP(-KE*TPD)
DUM2 = X1*ETA(11) + X2*ETA(12) +
   X3*ETA(13)
ARG = 15*(DUM2 + THETA(5))
COMP = EXP(ARG)/(1 + EXP(ARG))
OBSCNT = COMP*DOSE*KA/V/(KA-KE)*
   (OBSKE - OBSKA)
;PREDICTED VALUES
F1 = TDTR
F2 = SSCNT + OBSCNT
IF (CMT.EQ.1) THEN
Y = F1 + ERR(1)
ENDIF
IF (CMT.EQ.2) THEN
Y = F2 + ERR(2)
ENDIF
$THETA
(0, 0.3, 0.4); THETA1, KA
(2.5, 2.85, 3.); THETA2, CL
(50, 60, 80); THETA3, V
(11, 11.5, 13); THETA4, DOSE TIME
(0.4, 0.5, 0.6); THETA5, OFFSET FOR DOSE
   ADJUSTMENT
$OMEGA 0.075; OMEGA1, CLEARANCE
$OMEGA 0.1; OMEGA2, VOLUME
$OMEGA 0.7; OMEGA3, SUBJECT-SPECIFIC DOSE
   TIME EFFECT
$OMEGA BLOCK(1) 0 FIXED; OMEGA4,
   OCCASION-SPECIFIC DOSE TIME EFFECT
$OMEGA BLOCK(1) SAME; OMEGA5
$OMEGA BLOCK(1) SAME; OMEGA6
$OMEGA 0 FIXED; OMEGA7, SUBJECT-SPECIFIC
   STEADY-STATE EFFECT
$OMEGA BLOCK(1) 0.03; OMEGA8,
   OCCASION-SPECIFIC STEADY-STATE EFFECT
$OMEGA BLOCK(1) SAME; OMEGA9
$OMEGA BLOCK(1) SAME; OMEGA10
$OMEGA BLOCK(1) 1. FIXED; OMEGA11,
   OCCASION-SPECIFIC COMPLIANCE EFFECT
$OMEGA BLOCK(1) SAME; OMEGA12
$OMEGA BLOCK(1) SAME; OMEGA13
$SIGMA 0.9 FIXED; SIGMASQ1, DOSE-TIME
   RESIDUAL VARIANCE
$SIGMA 49; SIGMASQ2, CONCENTRATION
   RESIDUAL VARIANCE
$EST METHOD = CONDITIONAL MAXEVAL = 9000
   PRINT = 5 NOABORT
```

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